REMARKS

The present response is intended to be fully responsive to all points of objection and/or rejection raised by the Examiner and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application is respectfully requested.

Applicants assert that the present invention is new, non-obvious and useful. Prompt consideration and allowance of the claims is respectfully requested.

Status of Claims

Claims 59-131 are pending in this application. In the June 20, 2007 Office Action, the Examiner contended that claims 59-131 comprise six separate, patentably distinct inventions and required restriction of the claims. In the September 12, 2007 Office Action, the Examiner withdrew his requirement for restriction.

Claims 59, 79, 80, 82-88, 89, 92, 102, 103, 105, 108, 110, 117, 118, 120-122 and 128-131 have been amended herein.

35 U.S.C. § 112 Rejections

In the September 12, 2007 Office Action, the Examiner rejected claims 59-78, 88-101, 106, 108-116 and 119-131 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. According to the Examiner, the claims are drawn to an oral dosage form comprising insulin, but the specification discloses only the delivery agent 4-CNAB.

In response, Applicants have amended the independent claims to incorporate therein either a recitation of the structure of the delivery agent 4-CNAB or the chemical name of the delivery agent 4-CNAB. The claims thus now recite the specific embodiment including insulin and the delivery agent 4-CNAB, for which the specification provides specific written description. Applicants respectfully request that the Examiner withdraw this rejection.

35 U.S.C. § 102 Rejections

The Examiner rejected claims 59-91 under 35 U.S.C. § 102(e) as being anticipated by Weidner et al. (International Patent Appl. Publ. No. WO 02/02509). The Examiner stated that,

under M.P.E.P. § 2112.01, if the composition is physically the same, it must have the same functional properties, such that, if the prior art teaches the identical chemical structure, the properties claimed are necessarily present. However, the Examiner also admitted that he could not determine whether or not the oral solid dosage form disclosed by Weidner et al. inherently possesses properties that anticipate the claimed invention, and the Examiner has instead shifted to Applicants the burden of proof that this is not so.

Applicants traverse this rejection. Claim 59 as amended, from which all of claims 60-91 depend, recites an oral dosage form comprising a dose of unmodified insulin and an effective amount of the delivery agent 4-CNAB of a specific formula, wherein said dosage form achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient as compared to an untreated diabetic patient. As set forth below, Applicants argue that the fact that the dosage form achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient as compared to an untreated diabetic patient is not inherently disclosed in Weidner et al. Applicants argue that the inventions claimed in claims 59-91 are thus not inherently disclosed in Weidner et al., such that Weidner et al. does not anticipate claims 59-91.

The Examiner alleges that Weidner et al. discloses a solid oral delivery capsule comprising zinc human recombinant insulin and the delivery agent compound 4-CNAB and a method of administering the composition to diabetic monkeys, as disclosed in Example 1g on page 20 and Example 2 on pages 22-24 of Weidner et al. The Examiner clearly admits that Weidner et al. does not teach that the oral dosage form is suitable for humans or that it yields the specific claimed effects upon oral administration to diabetic humans of Weidner et al. However, the Examiner states that "there is a reasonable expectation that the species would meet these additional functional limitations", and the Examiner has shifted to Applicants the burden of proof that the additional functional limitations are not necessarily inherently meet by the oral dosage form of Weidner et al.

To the contrary, Applicants contend, there is not a reasonable expectation that the solid oral delivery capsule disclosed in Weidner et al. would necessarily meet the additional functional limitations as claimed, namely that the solid oral delivery capsule disclosed in Weidner et al.

would not necessarily achieve a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient as compared to an untreated diabetic patient. In this regard, it is important to note that Weidner et al. does not provide sufficient evidence to show that the specific claimed effects of claim 59 would necessarily result from oral administration to diabetic humans of the oral dosage form of Weidner et al.

Weidner et al. discloses, in Example 1g on page 20, a solid oral delivery capsule comprising zinc human recombinant insulin and the delivery agent compound 4-CNAB. Weidner et al. also discloses, in Example 2 on pages 22-24, a method of administering the composition to non-diabetic rats (Example 2A, at pages 21-22) and non-diabetic monkeys (Example 2B, pages 22-24). With respect to administration of the oral delivery capsule to rats, Weidner et al. disclosed only determination of the subject rats' serum insulin levels, and with respect to administration of the oral delivery capsule to monkeys, Weidner et al. disclosed only determination of the subject monkeys' serum insulin levels and blood glucose reduction.

Specifically, contrary to the contentions of the Examiner, the animal studies as described in Weidner et al. were not performed on diabetic animals. In fact, there is no disclosure whatsoever in Weidner et al., either in the cited examples or elsewhere, that the rat and monkey subjects of the insulin-4-CNAB dosage form studies had any form of impaired glucose tolerance, much less were diabetic. In addition, Weidner et al. did not disclose any analysis of these subjects or of these subjects' blood samples beyond determination of the subject non-diabetic rats' serum insulin levels and the subject non-diabetic monkeys' serum insulin levels and blood glucose reduction.

Moreover, Weidner et al. did not provide any analysis of administration of this composition to any other animal subjects, including diabetic animals. Furthermore, Weidner et al. most certainly did not make the jump in analysis to provide any suggestion regarding administration of this composition to humans, in particular to diabetic humans. As such, while Weidner et al. determined that oral administration of 4-CNAB with human insulin to some non-diabetic animals resulted in absorption of human insulin and a reduction in blood glucose levels, Weidner et al. is silent as to the effects of such administration upon diabetic animals and is silent as to the comparative effects of the composition on diabetic rats or monkeys. Weidner et al. is

also silent on the effects of such administration upon non-diabetic humans, as well as on the effects of such administration upon diabetic humans, and certainly on the comparative effects on diabetic humans as required in claim 59.

Despite this, the Examiner contends that there is a reasonable expectation that the composition disclosed in Weidner et al. would meet the additional functional limitations of claim 59. Thus, the Examiner contends that it would be reasonable to expect that the insulin-4-CNAB dosage form disclosed in Weidner et al. as having been administered to non-diabetic rats and monkeys would achieve a therapeutically effective reduction in blood glucose after oral administration to a diabetic human patient as compared to an untreated diabetic human patient. Applicants contend that such "reasonable expectation" is merely speculative, without Weidner et al. having disclosed any experiments on diabetic animals and most certainly without experiments on human subjects, whether non-diabetic or diabetic.

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). As discussed in M.P.E.P. § 2112, "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic", citing *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). Moreover, the Federal Circuit has stated that, in order to establish inherency, "the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

However, here, Weidner et al. does not provide sufficient disclosure to make clear that the disclosed composition is inherently capable of yielding a therapeutically effective reduction in blood glucose after oral administration to diabetic animals. Even more so, Weidner et al. does not provide sufficient disclosure to make clear that the disclosed composition is inherently

capable of yielding a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient as compared to an untreated diabetic patient. The Examiner has not even alleged that the results of claim 59 obtained by Applicants after administration of the oral dosage form to diabetic human subjects, i.e., a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient as compared to an untreated diabetic patient, would necessarily have been recognized at the time of the prior art reference as being able to be obtained by the same dosage form used in the prior art as was administered to non-diabetic non-human animal subjects.

M.P.E.P. § 2112 also advises that "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." In *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004), the Federal Circuit explained that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species. In this case, the Examiner stated that, because the chemical structure of the oral solid dosage form taught by Weidner et al. is identical to the claimed invention, there is a reasonable expectation that the species would meet these additional functional limitations.

To the contrary, Applicants contend that, simply because Weidner et al. discloses the broad genus of the composition and the species of administration to non-diabetic animals, Weidner et al. still does not necessarily disclose the species of how that composition would perform when administered to diabetic human subjects in comparison to non-treated diabetic human subjects. Applicants contend that Weidner et al. merely invites further experimentation to find out how the described oral solid dosage form would perform when administered to diabetic human subjects in comparison to non-treated diabetic human subjects, since there is no reasonable expectation that similar results obtained when administered to non-diabetic animal subjects would also have been obtained when administered to diabetic human subjects.

The Examiner, referring to M.P.E.P. § 2112, contends that "there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of

invention, but only that the subject matter is in fact inherent in the prior art reference." In response, Applicants refer the Examiner to the same M.P.E.P. § 2112, which cites *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) as stating that "the fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention." (emphasis supplied) In this regard, it is clear from the M.P.E.P., e.g., at §§ 2112 and 2121.01, that the cited prior art reference used to anticipate claims must be sufficiently described and enabled. According to the Federal Circuit, the disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter, and mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003). The Federal Circuit in *Elan Pharm.* cited *In re Donohue*, 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed. Cir. 1985), which stated that "even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it is not enabling."

However, as set forth below, Weidner et al. is not sufficiently described and enabled with respect to how that composition would perform when administered to diabetic human subjects. According to M.P.E.P. § 2164.01(a), the following factors set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), must be considered when determining whether a disclosure satisfies the enablement requirement for a particular set of claims, including: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In this situation, the prior art, not Applicants' claims, is being evaluated for enablement.

It is generally well accepted that the field of biotechnology, wherein the level of skill in the art is relatively high, is highly unpredictable in nature and mandates a heightened enablement disclosure. For inventions in the field of biotechnology, therefore, the crucial issue as to whether an invention is enabled is whether any experimentation necessary to practice the invention is

"undue". Applicants contend that it would have required undue experimentation for one of skill in the art at the time of this invention to determine how the composition disclosed in the prior art Weidner et al. reference would perform when administered to diabetic human subjects in comparison to non-treated diabetic human subjects. In support, Applicants herewith submit a Declaration of Shingai Majuru Under 37 C.F.R § 1.132, wherein Dr. Majuru, a Ph.D. in Pharmaceutics and the current director of Pharmaceutics and Research and development at Emisphere Technologies, Inc.

In the Declaration of Shingai Majuru, Dr. Majuru concludes that it would generally require undue experimentation for one of skill in the art to determine how a particular composition would perform when administered to diabetic human subjects in comparison to untreated human subjects based upon knowledge of how that particular composition would perform when administered to non-diabetic animal subjects. Specifically, Dr. Majuru concludes, based upon his knowledge and skill in the relevant field, that, based upon the disclosures as published in WO 02/02509, no conclusion may be drawn with regard to whether the solid oral delivery capsule disclosed in WO 02/02509 is inherently capable of yielding a therapeutically effective reduction in blood glucose after oral administration to diabetic human patients in comparison to untreated diabetic human subjects, as claimed in claims 59-91 as amended.

Accordingly, in view of the arguments above, Applicants have successfully met the Examiner's shifted burden of proof and have shown that the additional functional limitations as claimed are not necessarily inherently meet by the oral dosage form of Weidner et al. Thus, Applicants respectfully request that the Examiner withdraw this rejection of amended claims 59-91 under 35 U.S.C. § 102(e) as being anticipated by Weidner et al.

35 U.S.C. § 103 Rejections

The Examiner also rejected claims 92-131 under 35 U.S.C. § 103(a) as being unpatentable over Weidner et al. Applicants traverse this rejection.

Applicant note that Weidner et al. is an international application filed on June 29, 2001 that designated the U.S. and claimed priority to June 28, 2000 but published on January 10, 2002, which is subsequent to Applicants' claimed priority date of January 9, 2002. In

accordance with M.P.E.P. § 706.02(f)(1), this reference is available as prior art against Applicant's claims under 35 U.S.C. § 102(e). (In fact, as discussed above, the Examiner rejected claims 59-91 under 35 U.S.C. § 102(e) as being anticipated by Weidner et al.)

However, Applicants point out that 35 U.S.C. § 103(c) provides that "Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person." Accordingly, a reference that is prior art to the application under 35 U.S.C. 102(e) is disqualified from being used to reject the claims of the application under 35 U.S.C. 103(a) if that subject matter and the claimed invention "were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person."

In this case, both the Weidner et al. reference and the presently claimed invention are, and were at the time that this invention was made, owned by Emisphere Technologies, Inc. Accordingly, under 35 U.S.C. § 103(c), the Weidner et al. reference is disqualified from being used as a reference against the claims of this application, and Applicants respectfully request that the Examiner withdraw the rejection of claims 92-131 under 35 U.S.C. § 103(a).

Double Patenting Rejections

Claims 92-131 were provisionally rejected for obviousness-type double patenting over claims 1-29, 33-38 and 40-59 of U.S. Patent Appl. No. 10/541,433.

Claims 59-131 were provisionally rejected for obviousness-type double patenting over claims 1-92 of U.S. Patent Appl. No. 11/072,941.

Claims 59-131 were provisionally rejected for obviousness-type double patenting over claims of U.S. Patent Appl. No. 11/204,778.

Applicants note that these rejections are provisional, as none of the cited applications has issued as a U.S. patent. In response, Applicants are willing to file Terminal Disclaimers to

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disclaim the term of any patent to be granted off this application beyond the term of any patent to be granted on any of the cited applications.

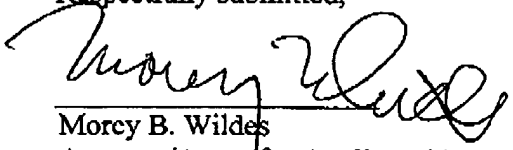
Conclusion

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,



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